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10/519,580	07/11/2005	Syed V.S. Kashmiri	4239-66176-05	3640

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KLARQUIST SPARKMAN, LLP  
121 S.W. SALMON STREET  
SUITE #1600  
PORTLAND, OR 97204-2988

EXAMINER
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BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1643

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

<b>Application No.</b> 10/519,580	<b>Applicant(s)</b> KASHMIRI ET AL.
<b>Examiner</b> David J. Blanchard	<b>Art Unit</b> 1643

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 29 December 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 + 1 months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.  
 Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: 20, 68-75 and 80-85.  
 Claim(s) objected to: 3 and 67.  
 Claim(s) rejected: 1, 2, 4, 8, 10-12, 16, 23-28 and 52.  
 Claim(s) withdrawn from consideration: 32-35, 44, 45, 47, 48, 76-79 and 86-89.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.  
 12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_  
 13. ☐ Other: \_\_\_\_\_.

/David J Blanchard/  
Primary Examiner, Art Unit 1643

Continuation of 5. Applicant's reply has overcome the following rejection(s):

The objection of claims 80 and 83 (claim 82, not 83) in the recitation "H-CDR3of", which should be corrected to "H-CDR3 of" is withdrawn in view of the amendments to the claims.

The objection of claim 6 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the cancellation of the claim.

The rejection of claims 23-28, 67-75 and 80-85 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "HuCC49V10" in claims 23, 67-68, 70, 80 and 82 as the sole means of identifying the parent antibody is withdrawn in view of the amendments to the claims.

The rejection of claims 3, 6, 68 and 80 under 35 U.S.C. 112, first paragraph, as lacking enablement is withdrawn in view of applicants' arguments, the amendments to the claims, which now clearly identify the parental HuCC49V10 antibody contributing the CDRs and in view of the cancellation of claim 6.

Continuation of 11. does NOT place the application in condition for allowance because:

The rejection of claims 1-2, 4, 8, 10-12, 16, 23-28 and 52 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claims (e.g., item no. 11 of the Office Action mailed 8/27/08) is maintained.

The rejection is maintained as it pertains to the claimed humanized CC49 antibody and antigen-binding fragments thereof (e.g., HuCC49V10) comprising a non-conservative amino acid substitution at any position OR at any tyrosine residue of L-CDR3 and wherein the humanized CC49 antibody has a high binding affinity for TAG-72, compared to a parent CC49 antibody, or a humanized CC49 antibody (e.g., HuCC49V10) comprising CDRs and human framework regions, wherein at least one CDR is a human antibody CDR and remaining CDRs are murine CC49 antibody CDRs and wherein the humanized CC49 antibody comprises a non-conservative substitution at any residue in the L-CDR3 and a substitution at any residue in any L-CDR or H-CDR of the antibody; wherein the humanized CC49 antibody has a high binding affinity for TAG-72 and is minimally immunogenic, compared to a parent CC49 antibody.

Applicants' arguments have been fully considered but are not persuasive. Applicants again argue that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction the experimentation should proceed. Applicant states that the CC49 and HuCC49V10 antibodies are described in the instant application and were well known at the time of filing. Further, applicant points out that the specification teaches and provides working examples (e.g., see citations at pg. 15 of the reply filed 5/28/08 and copies therewith). Applicant concludes that based on the teachings in the specification and the knowledge of the skilled artisan, it would be simply a matter of routine experimentation to make the humanized CC49 antibodies having the claimed genus of residue substitutions and to test these antibodies for their binding affinity and immunogenicity. This is not persuasive because as stated in the previous office action the teachings, guidance and exemplification in the specification are limited to two mutants of HuCC49V10, e.g., HuCC49V14 and HuCC49V15, which showed significantly higher antigen binding affinity and lower sera reactivity compared to the parental HuCC49V10 antibody. The specification discloses that the dissociation rates of only 6 isolated were lower than that of the parent antibody (HuCC49V10) as shown in Table 5 (Page 44, in particular) and the ELISA results show that the antigen-binding activity of only the two variants, HuCC49V10-14 and HuCC49V10-15, were either comparable to or exceeded that of the parental HuCC49V10 (page 47, in particular). Further, in Table 5, the relative affinity binding of CC49 antibodies show that only HuCC49V10-14 and HuCC49V10-15 exhibited a better/higher binding activity compared to the parent HuCC49V10; and the Flow cytometric analysis, in figure 6, showed that only two variants, HuCC49V10-14 and HuCC49V10-15 show significantly better binding to the cells displaying TAG-72 on their surface (page 50, in particular). In addition, the studies in regard to the sera reactivity of HuCC49V10 variants indicated that only HuCC49V10-14 and HuCC49V10-15 showed not only significantly higher antigen binding affinity that that of HuCC49V10, but they also showed much lower reactivity to sera from patients who showed an anti-idiotypic response to the parental CC49 antibody (page 53, in particular). Thus, while one skilled in the art may be able to synthesize and screen a variety of variants, based on the guidance and direction, one of ordinary skill in the art would have a low expectation of success and be forced into undue experimentation to make and use a humanized CC49 antibody having the requisite binding affinity and reduced immunogenicity. The specification does not disclose the genus of CC49 antibody variants wherein the L-CDR3 comprises just any a non-conservative amino acid substitution, or just any tyrosine to proline substitution, and optionally further comprising a substitution of a second residue in any heavy or light chain CDR, wherein the resulting CC49 variant has high binding affinity and a minimal immunogenicity compared to the parental HuCC49V10. Thus, the teachings guidance and exemplification provided in the specification is limited relative to the broad scope of the claims art issue.

Additionally, it is reiterated that the language of claim 23 and claims depending therefrom broadly embraces humanized CC49 antibodies that comprise one, two, three, four or five human CDRs in combination with as few as one CC49 CDR, i.e., "at least one CDR is a human antibody CDR..." is open claim language that is inclusive to up to five human CDRs in the humanized CC49 antibody. While applicant has demonstrated that HuCC49V10 comprising the L-CDR1 and L-CDR2 regions from the human LEN antibody, wherein the HuCC49V10 retains the antigen specificity of the parental CC49 antibody (TAG-72), applicant has not demonstrated that humanized CC49 antibodies comprising just any human L-CDR1 and L-CDR2 or comprising only one, two or three CC49 CDRs would maintain the binding characteristics of the parental CC49 antibody. Those of skill in the art recognize that "humanizing" antibodies routinely involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see Bendig of record, PTO-892 mailed 12/28/07). Thus, the state of the art recognized that it would be highly unpredictable that a humanized antibody comprising less than all six CDRs of a parental antibody with a desired specificity would retain the antigen-binding function of the parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the function of binding antigen includes six CDRs (three from the heavy chain variable region and three from the light chain variable region) from the same parental antibody in the context of framework sequences which maintain their correct spatial orientation have the requisite antigen-binding function. Therefore, one of skill in the art could not predictably extrapolate the teachings in the specification limited to HuCC49V10 comprising murine CC49 CDRs except that L-CDR1 and L-CDR2 are replaced with the corresponding human LEN L-CDR1 and L-CDR2 regions wherein HuCC49V10 retains the TAG-72 specificity and wherein two variants of HuCC49V10, V14 and V15, further comprise a tyrosine to proline substitution at Kabat position 91 in L-CDR3 (V14) and further comprise the tyrosine to proline substitution at Kabat position 91 in L-CDR3 and a valine to leucine substitution at Kabat position 27b in L-CDR1 (V15), which retain the TAG-72 antigen specificity to humanized CC49 antibodies comprising just any human L-CDR1 and L-

CDR2 or comprising only one, two or three CC49 CDRs would maintain the binding characteristics of the parental CC49 antibody.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al and Bendig M. M., (all of record) the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed antibody variants that retain the parental TAG-72 specificity for the treatment of cancer, with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed humanized antibodies and absent working examples providing evidence which is reasonably predictive that the claimed humanized antibody variants bind TAG-72, commensurate in scope with the claimed invention.

Claims 3 and 67 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Respectfully,  
David J. Blanchard  
571-272-0827